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A historical approach to the ventricular system of the brain

Una aproximación histórica del sistema ventricular en el sistema nervioso central

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| Abstract |

Introduction: The ventricular system of the brain was first described, partially, in the third century BC. Since then, several researchers have contributed to better understand this system, unraveling its position in the central nervous system, and relating it with certain functional aspects following philosophical concepts that have allowed a clearer approach to cavitations regarding the formation of the cerebrospinal fluid.

Objective: To describe the most relevant concepts of the history of the ventricular encephalic system of the brain.

Materials and methods: Various literature sources related to the ventricular system were consulted, and then chronologically organized, so that a more concrete approximation of the functional morphology of the ventricular system could be provided.

Conclusion: Aristotle was the first to approach the ventricular system of the brain. Over time, his knowledge on the organization, function and number of cavities was debugged to the point of proposing the existence of eight ventricles. Today, five ventricles are recognized, four of which are encephalic components: two in the brain, one in the diencephalon, other in the brainstem, and a fifth in the terminal part of the spinal cord.

Keywords: Cerebrum; History; Cerebrospinal Fluid; Neuroanatomy (MeSH).

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| Resumen |

Introducción. El sistema ventricular encefálico se conoció, con parcialidad, en el siglo III a.C., fecha desde la que diversos investigadores contribuyeron a una mejor comprensión de dicho sistema, desentrañando sus ubicaciones en el sistema nervioso central y relacionándolos con ciertos aspectos funcionales que surgieron de conceptos filosóficos. Esto permitió un acercamiento más objetivo hacia las cavitaciones relacionadas con la formación de líquido cerebroespinal.

Objetivo. Referenciar, de forma cronológica, los conceptos más trascendentes de la historia del sistema ventricular encefálico.

Materiales y métodos. Se consultaron diversas fuentes bibliográficas relacionadas con el sistema ventricular, para después ordenarlas según su cronología, de modo que se concluyera con una aproximación más concreta de la morfología funcional del sistema ventricular.

Conclusión. Aristóteles fue el primero en abordar el sistema ventricular encefálico, de modo que, conforme el paso de los años, su conocimiento se fue depurando en cuanto a organización, función y número de cavidades, hasta llegar a proponer la existencia de ocho ventrículos. En la actualidad se reconocen cinco ventrículos, de los cuales cuatro son componentes encefálicos: dos en cerebro, uno en diencéfalo, otro en tronco encefálico y un quinto en la parte terminal de la médula espinal.

Palabras clave: Encéfalo; Historia; Líquido cefalorraquídeo; Ventrículos encefálicos (DeCS).

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Introduction

The history of the ventricular system

Aristotle (384-322 BC) was perhaps the first person to report the existence of brain cavities, particularly those located in each cerebral hemisphere. He pointed the presence of a small hole in the center of the brain in most of the animals he studied (1). However, Herophilos of Chalcedon (335-280 BC), a Greek physician and precursor of teaching and learning of human anatomy, was the real discoverer through the first dissections in human cadavers following the scientific rigor of his time (2), which allowed him to identify and describe such ventricles (3,4). He also described the choroid plexuses (5,6) as constituent elements of these chambers, and thought that the pineal organ was some sort of valve capable of closing the cerebral aqueduct to prevent the passage of *pneuma psykhikon (spiritus animalis)* to the posterior ventricle, where memory was believed to exist, acting as a guardian of psychic activity (7).

Around that time, Erasistratus of Ceos (304-250 BC), a disciple of Herophilus, proposed the ventricular theory to explain the function of the pneuma. He stated that the *pneuma zoticon (spiritus vitalis)*, found in the blood, extended from the heart to the brain, and turned into *pneuma psykhikon* in the lateral ventricles (5,8,9), controlling structure-function relationships until traveling through the motor nerves to the muscles (3,10).

Although Herophilus and Erasistratus are credited with the identification of the cerebral ventricles, Rufus of Ephesus (110-180), teacher of Galen of Pergamum, detailed the lateral ventricles —the third and fourth ventricles— and the mesencephalic aqueduct (11). Similarly, Galen (130-200) described this ventricular system with detail and believed in the presence of pneuma, conceived as a breath emanated from the cosmos that circulated through these cavities, serving as a mediator between body and soul. In addition, he considered that the superior vermis of the cerebellum acted as a valve to prevent the passage of *pneuma psychicon* to the posterior ventricle (12), and that seizures were originated by the obstruction of the exit of the cerebral ventricles.

Galen not only provided a correct view of the morphology of the four ventricles by dissecting oxen encephala, but also found that the anterior ventricle was even (9) and that the mental faculties were located in the solid portions of the brain. In 390, Nemesius of Emesa refuted this idea, and claimed that all mental faculties were located inside the ventricles and that, following the antero-posterior pattern proposed by Posidonius of Byzantium, they could be observed through lesions in different cerebral regions (14). For example, injuries to the anterior ventricle of the brain impaired fantasy and imagination, whereas lesions in the posterior region affected memory and, if damage occurred in the middle portion, reasoning was altered (1,15). This tricameral functional pattern was preserved for several centuries (1) until the Renaissance, when Leonardo da Vinci and Andreas Vesalius challenged this idea.

In *Anathomia*, written in 1316, Mondino de Luzzi (1270-1326) maintained the tricameral theory (16) for cerebral ventricles (Figure 1) and, although he contributed his own ideas to anatomy based on his observations of human dissections, he followed the Galenic tradition in his work. On the other hand, Mondino proposed, as a new element, that the choroid plexus was the valve that regulated the flow of *spiritus animalis* (12). Accustomed to iterate the dogmas of Greek and Latin academic authorities generated by the school of Hippocrates and the teachings of Galen, the classical academic tradition prevailed without any relevant demonstrations or conceptual advances about the ventricular system.

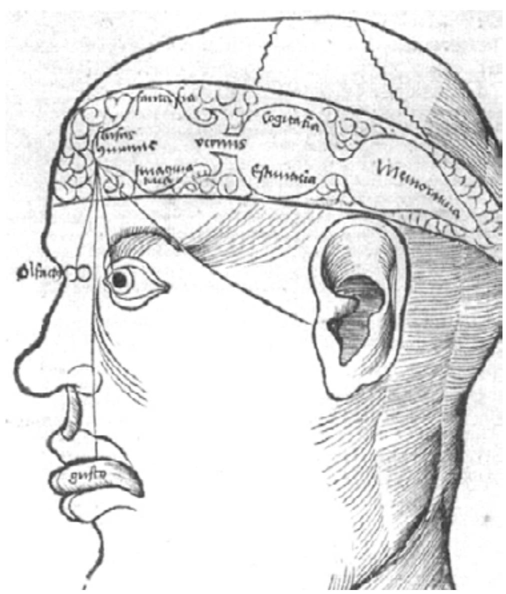

Figure 1. Gregord Reisch's scheme (1503), which shows the typical medieval conception of the human brain and its tricameral composition. Source: Own elaboration based on Martensen (27).

Then, this tradition was subverted by Leonardo da Vinci (1452-1519) and his first anatomical drawings, which date back to around 1487 (17). Da Vinci's drawings are of admirable clarity, despite having some errors, and reflect his wish to delve into the mechanisms of the most intimate functions and relations of the deepest organs, such as the brain ventricles. He stated in his notes that the anatomy of the brain had two vents in the large ventricles, in which molten wax was injected to fill the cavities of the brain. Once the wax hardened, it was removed from the brain to see the exact shape of the three ventricles (12,15,18,19). Thus, da Vinci extracted a mold that showed the three-dimensional shape of the ventricular labyrinth in the brain of an ox (15), and made the first realistic drawing of the cerebral ventricles (15,20,21). This greatly coincided with what is now known about the ventricular system, since his drawings showed at least the occipital horns of the lateral ventricles.

Nevertheless, da Vinci could not identify the temporal horns of these ventricles due to the absence of openings to access them and the use of unpreserved brains. Also, in his notes on the ventricular system, he thought that the spinal cord ended in the fourth ventricle, and concluded that the sense of touch went through there (15), opposing the ideas about the flow of pneuma.

Afterwards, such wax mold was extrapolated to humans, which can be observed when comparing W19127r and Schlossmuseum paints (Figure 2). The wax technique was not used again until the seventeenth century by Ruysch (15).

Figure 2. The four encephalic ventricles at the top. Leonardo da Vinci's drawing. Source: (22).

Furthermore, the great anatomist Andreas Vesalius (1514-1564), contemporary of Leonardo, came to conclusions that contradicted established galenic dogmas by means of dissections made in executed criminals. For example, he noted that the structure of the brain was different from that of Galen, and that the brain ventricles did not contain any *spiritu*, but were filled with a clear fluid, later called *cerebrospinal fluid* (CSF). References of this clear fluid inside the skull had already been made in the past; in a papyrus dating from the seventeenth century BC, a skull fracture is described in the occipital region with a fluid leak (23).

Vesalius also rejected the idea of Herophilus, in which the pineal organ was a kind of valve capable of closing the cerebral aqueduct (9). Around that date, Juan Valverde de Amusco (1525-1588), Spanish physician and anatomist, indicated in his in History of the composition of the human body (seventh book) that the brain tissue has four ventricles, known as ventrezillos, interconnected by the mesencephalic aqueduct, which is described as a small brook (24).

Similarly, Giulio Cesare Casserius (1552-1616), an anatomist from Padua, discovered the arachnoid granulations (25) where CSF passes into the venous circulation. These granulations were described in 1705 by Antonio Pacchioni (1665-1726) in his work *Dissertatio epistolaris de glandulis conglobatis dura e meningis humanae, indequeortis lymphaticis ad piammeningem*, through which CSF flows into the venous sinuses (26).

Thomas Willis (1621-1675), a century after Vesalius, proposed that CSF originated in the choroid plexus, inside the ventricles, and that it circulated through these cavities and preserved body heat through blood (1). In that same century, René Descartes (1596-1650) hypothesized that the fluid in the brain ventricles was under pressure and that the pineal organ turned in a particular direction when the mind decided to perform a certain action, causing the flow to move from the brain to the nerves. In consequence, such flow was the cause of the movement (27-28) in different directions to facilitate the distribution of the spirits (29). Thus, Descartes supported the concept of *spiritus animalis* of Galen (20). On the other hand, his contemporary Niels Stensen (1638-1686) refuted this hypothesis and, through careful dissection, revealed the correct position of the pineal organ, proving that it was a fragile structure fixed directly to the brain, which tended to break easily if it was moved; therefore, it could not produce movement as Descartes stated (29).

In 1851, Andrea Verga (Italy, 1811-1895) described a posterior prolongation that he called *cavum septum pellucidum* (30), a triangular space whose base is attached superiorly to the corpus callosum, and runs as a sheet down to the fornix (31). Over time, this region was known as *cavum vergae* or sixth ventricle. It is located in the midline of the brain, and its name does not indicate anything about its nature (32). In recent years, it has been established that the *cavum* does not have the characteristics of a true ventricle, since it does not have an ependymal lining (33) and lacks CFS, although it is hypothesized that the liquid found there derives from neurons and glial cells (34).

In 1859, Stilling (1810-1879), German anatomist and surgeon, was the first to describe the terminal ventricle as a cystic cavity lined by ependymal cells, located in the conus medullaris (35), which was, at that moment, the seventh ventricle. Then, in 1875, Krause identified it as a true ventricle, delimited by ciliated ependymal cells, and called it the fifth ventricle (36). In his honor, the eponym Krause's ventricle was used. In 1924, Kernohan performed complete anatomical studies and determined that it usually appears during the embryonic development of the marrow, but that it tends to disappear after birth or may persist as a residual ependymal tissue (37). Even so, Anatomic Terminology includes this ventricle as one more element of the ventricular encephalic system, with the reference A14.1.02.006 (38).

Another element that was associated with the CFA is the interposed veil cistern. It is a retreat of the pia mater found between the roof of the third ventricle and the fornices, a location that usually presents as a small triangular subarachnoid space. However, when this cistern is enlarged, as a result of the abnormal separation of the fornix pillars, it is called cavum of the interposed veil (39).

So far, throughout history, up to eight saccular dilations have been associated with the ventricular system; three of them correspond to subarachnoid dilatations, while the remaining five are ventricles that derive from the normal development of the neural tube.

In the end, the mechanical hypothesis that the pineal organ was a regulating element in the flow of animal spirits was rejected and modified by Magendie (1783-1855), who proposed that a flow of CFS occurred there (40). On the other hand, diagnosis by lumbar puncture to obtain CFS was not introduced until 1891 by the neurologist Quinke (1842-1922) (41), who expanded the field of medical understanding about the conditions associated with CFS through its application to clinical events.

The ventricular system: current concept

Today, Anatomical Terminology accepts that the ventricular system is made up of a series of dilatations, orifices and ducts and that the central nervous system is a part of it (38). The neuroanatomical description of the latter, complemented by neuro-navigation techniques (42), confirms that four ventricles are located in the brain region: two lateral ventricles located in the brain, a third ventricle in the diencephalon, and the fourth ventricle located behind the encephalic trunk. In addition, there is a fifth ventricle in the terminal part of the spinal cord, known as terminal ventricle (38). The four brain ventricles are interconnected by the interventricular foramina and the cerebral aqueduct, so the fourth ventricle also establishes direct communication with the subarachnoid space through two lateral foramina and one medial foramen (42,43). Finally, the medullary region is traversed longitudinally, discontinuously or closed to the stretches (44) through the central conduit or epindemal cell, which ends in the fifth ventricle (35) or caudal apex in smaller vertebrates (45).

Also, the ventricular system has elements associated with the formation and circulation of CFS, which is produced continuously and is subjected to circadian rhythms through mechanisms operated by sympathetic cholinergic innervation, receptors in the choroid plexus for dopamine, serotonin, melatonin and neuropeptides, such as vasopressin, atrial natriuretic polypeptide and angiotensin II (45). This allows the permanent production of CFS, which oscillates between 100 mL and 150 mL in young adults; approximately 30 mL are found inside this ventricular system (40,46,47).

The production of CFS is estimated at about 500mL per day (40,46-48), of which about 70-80% —in other words, 350-400 mL equivalent to 350 microliters per minute— is produced in the choroid plexus (49) thanks to mechanisms involving passive transports such as osmosis and diffusion, and active transports such as transcytosis, including endocytosis and exocytosis. In addition, due to the lack of an ependymal barrier between the extracellular fluid and CFS, some substances in the cerebral parenchyma may be the main source of non-choroidal fluid, representing the remaining 10%-30% of the total CFS. Most of this fluid is removed permanently into the blood through the arachnoid villi, while a small portion is lymphatically removed via the nerve roots (49).

This cerebrospinal fluid plays an important role in the maintenance of homeostasis in the central nervous system, because it provides buoyancy of the brain and nerve roots, transports nutrients, peptides and proteins, regulates the brain volume through osmoregulation mechanisms, transports transducing signals to cells, and eliminates unnecessary substances and metabolites (50). Thus, it is known that several signaling molecules are directed from the blood to the cerebrospinal fluid, as is the case of spondine, transthyretin and fibroblast-derived growth factor. In addition, these molecules participate in the neurogenesis of stem cells, both in intrauterine and postnatal life (51).

Conclusions

Knowledge on the existence of ventricles in the central nervous system dates back to Aristotle. Three ventricles were initially proposed (anterior, middle and posterior), but the ideas, concepts and hypotheses about the ventricular system underwent modifications over time, in terms of chambers number, their organization and their function. At some point, even eight brain ventricles were proposed. Today, the existence of five ventricles in the human ventricular system is recognized: one is located in the terminal part of the spinal cord and the remaining four are located in the encephalon. With the exception of the terminal ventricle, the others are interconnected by foramen and ducts, through which cerebrospinal fluid circulates but not *spiritus animalis*, as ancient scholars thought.

Conflict of interest

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